REMARKS

As Applicants are filing a RCE herewith, this amendment should be entered and considered by the Examiner at this time.

Applicants have the following comments in support of this amendment and in response to the Final Rejection.

Claim Amendments – Reference to Disclosure

The claimed pharmaceutical compositions of the present application are directed to formulations of certain novel highly-halogenated halogenated xanthenes, including 4,5,6,7-Tetrabromoerythrosin, that the inventors have adapted into a chemotherapeutic pharmaceutical composition for chemotherapeutic application. The specification of the present application makes it clear that such halogenated xanthenes may be in either a non-derivative or a derivative form, as is clear from the following passage:

> "[0023] The present invention is directed to new chemotherapeutic medicaments ... wherein a primary active component of such medicaments is a *halogenated xanthene or halogenated xanthene derivative*." Page 5 (emphasis added).[1]

The identity of these forms is determined by the composition of the organic functionalities at positions R^1 and R^2, as illustrated by the following from the present application:

> "[0027] Selected chemical and physical properties (such as chemical constituents at positions X, Y, and Z and functionalities R^1 and R^2) of representative halogenated xanthenes are summarized in attached Table 1." Page 7.

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[1] See also [0047] - [0049] on p. 14-15 of the present application discussing halogenated xanthenes and halogenated xanthene derivatives.

Table 1 shows representative examples of the range of constituents that may be present at R^1 and R^2, including hydrogen atoms (i.e., if R^1 and R^2 are both hydrogen atoms, the halogenated xanthene is in its acid form), various monovalent cations (i.e., such as Na+ and K+, rendering the halogenated xanthenes as monobasic or dibasic salts when one or both positions R^1 and R^2, respectively comprise cations), and various organic constituents (i.e., an ethyl group, as per the example of ethyl eosin). Applicants note that when these molecules are at physiologic pH (i.e., 5-7), they are in the dibasic form (i.e., both hydrogen atoms at R^1 and R^2 are replaced with monovalent cations, as for instance in the listed examples of disodium rose bengal and disodium 4,5,6,7-tetrabromoerythrosin) due to there inherent chemical properties.

The aforementioned acid forms of the halogenated xanthenes, along with the example dibasic forms, constitute non-derivative forms of these molecules, while the forms having organic constituents at R^1 or R^2 are derivative forms. This standard nomenclature is further illustrated by the following passage from the present application:

> "[0045] Moreover, that the facility with which the halogenated xanthenes target specific tissues or other sites can be further optimized by *attachment of specific functional derivatives* at positions R^1 and R^2.... An example of this is esterification at position R^1 with a short aliphatic alcohol, such as n-hexanol, to produce a *derivatized agent* exhibiting enhanced partitioning into lipid-rich tumor tissues.
> "[0046] It is thus a further preferred embodiment that at least one of the at least one *halogenated xanthene active ingredients includes at least one targeting moiety* selected from a group that includes DNA, RNA, amino acids, proteins, *antibodies*, ligands, haptens, carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, encapsulating vehicles, short- or long-chain aliphatic or aromatic hydrocarbons, including those containing aldehydes, ketones, alcohols, esters, amides, amines, nitriles, azides, or other hydrophilic or hydrophobic moieties. A further

> example of this embodiment is derivatization of Rose Bengal with a lipid (at position R^1, via esterification), so as to increase the lipophilicity of Rose Bengal, and thereby modify its targeting properties in a patient...." Pages 13-14 (emphasis added).

This makes it clear that ethyl eosin (of Table1) is a derivative form of eosin. The passage also lists a range of example organic constituents that, if attached to position R^1 or R^2, render the halogenated xanthene a *halogenated xanthene derivative* (i.e., containing a functional derivative at position R^1 or R^2).

Therefore, it is clear that the present application discloses both non-derivative and derivative halogenated xanthenes in the present invention. Applicants are amending independent Claims 1 and 19 to be directed to the embodiment of the present invention consisting of non-derivative forms of the halogenated xanthenes. Specifically, by claiming only those halogenated xanthenes that contain only sodium (i.e., Na+), potassium (i.e., K+) or hydrogen (i.e., H) at positions R^1 and R^2, it is clear that the presently claimed invention does not encompass halogenated xanthenes that contain organic constituents at positions R^1 or R^2 but rather are directed to pharmaceutical compositions consisting of non-derivative halogenated xanthenes.[2]

In order to advance prosecution of the present applicant, Applicants are also amending independent Claims 1 and 19 so as to not recite certain fluorinated derivatives of the halogenated xanthenes. Such amendment is made without prejudice or disclaimer.

Applicants are also adding new independent Claims 36 and 37. Claim 36 combines the subject of amended independent Claim 1 and previously presented Claim 2 dependent thereupon.

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[2] Applicants are amending the claims to recite "wherein the functionalities at positions R^1 and R^2 each comprise an element selected from the group consisting of sodium, potassium and hydrogen." The recitation of the term "element" is being used as a general term and includes cations such as Na+ and K+.

Claim 37 further defines a subset of concentrations delineated in Claim 36, such concentrations are disclosed in the specification as filed at, for example, paragraphs [0036] and [0039]. If any fee should be due for these new claims, please charge our deposit account 50/1039.

Accordingly, Applicants respectfully submit that the amendments to Claims 1 and 19 are not adding any new matter and are clearly supported by the application as filed. Therefore, it is requested that they be entered and considered at this time.

Novel Composition of Matter

As Applicants explained in Amendment E, filed on May 23, 2005, amended independent Claims 1 and 19 are directed to various pharmaceutical compositions that contain certain highly-halogenated halogenated xanthenes, including 4,5,6,7-Tetrabromoerythrosin, none of which are believed to have been described in the prior art. These highly-halogenated xanthenes are particularly enriched with chlorine, bromine and iodine atoms in comparison with previously known halogenated xanthenes. Due to the relative complexity of synthesis of such compounds due to steric hindrance[3] from these atoms and other factors, such as stability considerations, Applicants believe they have invented new compounds which represent a novel extension to the halogenated xanthene family. Accordingly, Applicants respectfully submit that the claimed highly-halogenated halogenated xanthenes and the various claimed chemotherapeutic pharmaceutical compositions containing such

[3] Steric hindrance is spatial interference inhibiting or preventing the close arrangement of adjacent atoms within a molecule due to the sizes of the overlapping electron clouds of the adjacent atoms, and poses particularly difficult synthetic challenges when large atoms, such as chlorine, bromine and iodine, are incorporated into a molecule. In contrast fluorine, which is by far the smallest halogen, does not generally pose significant steric hindrance because its small electron cloud results in little interfering overlap.

highly-halogenated halogenated xanthenes of the claims of the present application are novel over the prior art.

Applicants will now address each of the Examiner's comments and rejections in the order in which they appear in the Final Rejection.

Priority

In the Final Rejection, the Examiner objects to the priority statement on page 1 of the specification. Applicants respectfully disagree with the Examiner's objection.

In particular, the application as filed states that the present application is a continuation-in-part of 09/635,276 filed on August 9, 2000. The amendment to the specification with regard to the '276 application is based on the Examiner's request in the prior Office Action. It is not believed that there should be any dispute as to this priority recital or the form of the recital.

Paragraph [0001] of the present application as filed also states that the '276 application is incorporated by reference in its entirety. The '276 application as filed includes a clear reference that the '276 application is a continuation-in-part of US application 09/216,787 filed December 21, 1998 (a copy of this page from the '276 application is attached). Accordingly, that reference is incorporated by reference in the present application.[4] In the amendment to the specification filed on November 18, 2005, Applicants were merely reciting that material which was previously incorporated by reference.

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[4] Paragraph [0027] on page 7 of the present application also incorporates by reference the '276 application and application no. 09/216,787.

Accordingly, Applicants respectfully submit that Applicants' amendment and priority information was proper and request that the Examiner enter this amendment.

Claim Rejections – 35 USC §102

The Examiner also rejects Claims 1, 9-11, 19 and 27 under 35 U.S.C. §102(e) as being anticipated by Dees et al. (US 6,331,286). This rejection is respectfully traversed for at least the following reasons.

In particular, the present application is a continuation-in-part of US application '276 which is a continuation-in-part of US application 09/216,787 (which became the Dees '286 patent). Hence, the present application claims priority back to Dees '286, and Dees '286 is not prior art to the present application.

Furthermore, whereas the radiosensitization methods of Dees are predicated on the presence of ionizing radiation and activation of a radiosensitizer (containing a halogenated xanthene) using applied ionizing radiation, the pharmaceutical compositions of the claimed invention avoids the necessity of applying radiation.[5] Instead, the claimed invention is directed to novel pharmaceutical compositions which are pharmacologically active against cancer and other diseased tissues without the necessity of additional activation. Such directly chemotherapeutic compositions have improved utility over the teachings in Dees as it is preferable to treat cancer and other diseased tissue with only one substance or step, i.e. the claimed compositions, rather than having to add additional activating energy, such as the ionizing radiation of Dees, to the body.

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[5] As explained by the Court of Appeals for the Federal Circuit in *Perricone v. Medicis Pharmaceutical Corp.*, 77USPQ 2D 1321, 1328 (Fed. Cir. 2005), the disclosure of a compound or method does not disclose all applications for that compound.

Finally, with respect to independent Claim 19, Dees does not disclose the claimed delivery vehicle or delivery of a medicinal composition formulated in a delivery vehicle consisting of a tablet, a capsule, or a suppository.

Accordingly, for at least the above-stated reasons, Claims 1, 9-11, 19 and 27 are patentable over Dees, and it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC §112

The Examiner also rejects Claims 1-2, 9-11, 19 and 27 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement, and apears to be objecting to the recital of certain specific halogenated xanthenes not containing a functional derivative at position R^1 and R^2. This rejection is also respectfully traversed.

While Applicants traverse this rejection and still believe that there is support for the objected to language, in order to advance the prosecution of this application Applicants have amended independent Claims 1 and 19, to remove the recital of "wherein said halogenated xanthene does not contain a functional derivative at position" and the recital of certain halogenated xanthenes. As explained above, the remaining recited halogenated xanthenes, wherein the functionalities at positions R^1 and R^2 comprise sodium, potassium or hydrogen, are clearly supported by the present application as filed.[6] Applicants respectfully submit that such amendments overcome the

[6] While Applicants are amending the claims to remove the language regarding non-derivative forms of the claimed halogenated xanthenes, independent Claims 1 and 19 are still patentable over Goers, Bottiroli and Schultz as explained in prior Amendment E as none of these references disclose or suggest the claimed pharmaceutical compositions that contain certain highly halogentated xanthenes such as 4,5,6,7-Tetrabromoerythrosin, nor do any of these references disclose or suggest the claimed pharmaceutical compositions that contain halogenated xanthenes containing only sodium, potassium or hydrogen at positions R^1 and R^2.

Examiner's stated reasons for the rejection of the subject claims under 35 U.S.C. §112, first paragraph.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Claim Rejections – 35 USC §102

The Examiner also rejects Claims 1, 9-11, 19 and 27 under 35 U.S.C. §102(b)as being anticipated by Gee et al. (WO 97/39064 A1). This rejection is also respectfully traversed.

As noted by the Examiner on p. 7 and 8 of the Final Rejection, Gee concerns certain compositions containing multiply-fluorinated halogenated xanthenes. Such subset of the halogenated xanthenes are purported by Gee to have utility as fluorescent dyes for certain in vitro tests. In contrast, the presently claimed compositions, which do not include *any* fluorinated halogenated xanthenes, are incorporated in chemotherapeutic pharmaceutical compositions which have been shown to have utility in vivo as medicinal agents for chemotherapeutic purposes. Knowledge that one subset of halogenated xanthenes, such as those described by Gee, has utility for in vitro diagnostic use would not lead one of skill in the art to conclude that a separate, unrelated subset of halogenated xanthenes would have suitable pharmacokinetic and pharmacodynamic properties, when appropriately formulated, to serve as the active component in chemotherapeutic medicinal agents.[7]

Further, as discussed *supra*, in order to advance the prosecution of this application, Applicants have amended the claims to remove the recital of any fluorinated halogenated xanthenes.

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[7]See e,g, *Perricone,* 77USPQ2D 1321, discussed *supra.*

As Gee does not disclose or suggest any of the remaining claimed halogenated xanthenes, the claims are patentable over Gee.

Accordingly, for at least the above-stated reasons, Gee does not disclose or suggest the presently claimed invention, and it is respectfully requested that this rejection be withdrawn.

Interview Request

If the Examiner still wishes to reject the claims of the present application after considering this amendment, then Applicants request an interview with the Examiner to discuss the rejections in further depth. Therefore, in order to advance the prosecution of this application, it is respectfully requested that the Examiner please contact the undersigned to set-up such an interview prior to the issuance of a further Office Action for this application.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable condition and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any further fee should be due for this amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: August 4, 2006

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Signature

IMPROVED TOPICAL MEDICAMENTS AND METHODS FOR PHOTODYNAMIC TREATMENT OF DISEASE

Inventors: H. Craig Dees, Timothy C. Scott, John T. Smolik, Eric A. Wachter and Walter G. Fisher

BACKGROUND OF THE INVENTION

This application claims the benefit of U.S. Provisional Application No. 60/149,015 filed August 13, 1999 which ~~is a c~~ontinuation-in-part of USSN 08/989,231, filed December 11, 1997, USSN 09/130,041, filed on August 6, 1998, USSN 09/184,388, filed on November 2, 1998, and USSN 09/216,787, filed on December 21, 1998, which are herein incorporated by reference in their entirety.

The present invention is related to certain photodynamic, topically-applicable medicaments and methods for treatment of human or animal tissue using photodynamic therapy (PDT).

PDT was originally developed to treat cancer and other diseases with the promise of limiting the invasiveness of the therapeutic intervention and lessening potential collateral damage to normal, non-diseased tissue. In its simplest form, PDT is the combination of a photosensitive agent with special forms of illumination to produce a therapeutic response in certain tissues, such as a tumor. The agent attains an excited, active state when it absorbs one or more photons and then is or becomes efficacious. Key elements of a successful PDT regimen include either selective application or selective uptake of a photosensitive agent into the diseased tissue and site-specific application of the activating light. PDT agents are typically applied systemically (for example, via intravenous injection or oral administration) or via localized topical application directly to diseased tissues (for example, via topical creams, ointments, or sprays). Subsequent to administration of the agent (typically 30 minutes to 72 hours later), an activating light is applied to the disease site, locally activating the agent, and destroying the diseased tissue. Light is typically applied by direct illumination of the site, or by delivery of light energy to internal locations using a fiberoptic catheter or similar device.

Most current PDT regimens are based on systemic application of porphyrin-based agents or topical or systemic application of psoralen-based agents. Examples of porphyrin-based agents include porfimer sodium (PHOTOFRIN®), hematoporphyrin-derivative (HPD), benzoporphyrin derivative